REMARKS

Claims 1 and 38 have been amended. Claims 11, 12, 40, and 41 have been canceled. Claims 1-10, 13, 38, and 39 remain in the application.

Support for the amendment to Claim 1 is found, for example, in the specification at page 7, lines 12-13; page 18, lines 20-21; page 1, lines 17-20; page 5, lines 20-21; page 15, lines 11-14; page 21, lines 5-18; page 21, lines 23-24; and page 16, line 21.

Some of the amendments to Claim 1 are intended to change the scope of the Claim, while others are intended only as clarifications that are not intended to change its scope. In particular, the amended clauses or phrases referring to "a particular tumor" or to "the angiogenic potential of a particular tumor" are intended to change the scope of Claim 1. All other amendments to Claim 1 are in the nature of clarifications that are not intended to change the scope of the Claim.

Claim 11 has been canceled as being redundant in view of the amendment to Claim 1.

Claims 12, 40, and 41 have been canceled as no longer being proper dependent Claims in view of the amendment to Claim 1. It is applicants' current intention not to abandon the subject matter of the canceled claims, however, but rather to present it in the co-pending divisional application.

Claim 38 has been amended to conform its language to that of amended Claim 1. No change in the scope of Claim 38 is intended.

It is believed that no fee is due to submit this paper. If a fee is due, please refer to the Deposit Account Authorization previously filed for this application. If any additional extension of time is required, please consider this paper a petition for the total extension of time required.

Reexamination and reconsideration of the application, as amended, are respectfully requested.

The Claim Objection

Claim 1 was objected to as containing an apparent typographical error, such as the use of a comma before the "and" in line 8 (now line 9). It is respectfully submitted that it is preferred usage to include a comma before a conjunction such as "and" in a series of three or more terms. The Office is referred, for example to page 2, rule 2 of Strunk and White, *The Elements of Style* (Third Edition 1979).

According to the undersigned's notes, a tentative agreement was reached at the October 7, 2003 Interview that this ground of objection should be withdrawn.

It is respectfully submitted that this ground of objection should be withdrawn.

The § 112, Second Paragraph Rejections

Claims 1-13, and 38-41 were rejected under 35 U.S.C. § 112, second paragraph on several grounds. The Office gave specific grounds of rejection only for Claims 1, 2, and 40, so it is assumed that the remaining Claims were rejected solely due to their dependence from independent Claim 1 or dependent Claim 40.

Claim 40 has been canceled, so the rejection of that Claim is now moot.

Claim 1

Claim 1 was said to be indefinite in the phrases "other cells of the tissue" and "including blood vessels, supportive stromal elements, neural cells, and endothelial cells." It is respectfully submitted that the clarification to the middle portion of part (a) of Claim 1 overcomes this ground of rejection. According to the undersigned's notes, a tentative

agreement was reached at the October 7, 2003 Interview that this clarification would overcome this ground of rejection.

Claim 1 was also said to be indefinite in the phrase "if any." It is respectfully submitted that the clarifications to Claim 1 to refer to -- any angiogenic vessels -- rather than to "angiogenic vessels, if any" overcome this ground of rejection. According to the undersigned's notes, a tentative agreement was reached at the October 7, 2003 Interview that this clarification would overcome this ground of rejection.

The Office also said that the limitation "time sufficient" was indefinite. It is respectfully submitted that the clarification to Claim 1 to refer to a -- time sufficient to allow any angiogenic vessels to grow -- rather than to a "time sufficient to allow angiogenic vessels, if any, to grow" overcomes this ground of rejection. According to the undersigned's notes, a tentative agreement was reached at the October 7, 2003 Interview that this clarification would overcome this ground of rejection.

Claim 2

Claim 2 was said to be indefinite in its use of the word "substantially." For the reasons previously given in the Applicants' September 5, 2003 Reply, it is respectfully submitted that the term "substantially," as used in Claim 2, is definite.

According to the undersigned's notes, a tentative agreement was reached at the October 7, 2003 Interview that this ground of rejection should be withdrawn.

§ 112, Second Paragraph Summary

It is respectfully submitted that all § 112, second paragraph rejections have been overcome or should be withdrawn.

The §§ 102 and 103 Rejections

All Claims were rejected under 35 U.S.C. §§ 102(b) and 103 as being both anticipated by, and obvious over, one or more of four different references cited by the Office.

For the reasons given in the September 5, 2003 Reply, it is respectfully submitted that the claimed inventions, even prior to the present amendment, were both novel and nonobvious over the cited references, whether those references were considered individually or in combination.

Nevertheless, in the interest of accelerating prosecution, independent Claim 1 has been amended to distinguish the cited references even more clearly. Claim 1 now refers, for example, to – assaying the angiogenic potential of a particular tumor in a mammal –. None of the cited references teaches or suggests such a limitation. (Please note that it is Applicants' current intention not to abandon the canceled subject matter, but rather to present it in the co-pending divisional application.)

According to the undersigned's notes, a tentative agreement was reached at the October 7, 2003 Interview that the present amendment to independent Claim 1 would overcome the § 102 rejections; and also that the amendment appeared likely to overcome the § 103 rejections as well. Examiners Afremova and Saucier noted that they would

consider the § 103 question further following the Interview; and also that an additional search would be conducted respecting amended Claim 1.

The Office is respectfully referred to the reasons given in the September 5, 2003 Reply for distinguishing Claim 1 from the four cited references. The same reasons continue to apply to Claim 1 as amended.

In addition, it is respectfully submitted that the amendment to Claim 1 even more clearly distinguishes it from the cited references. None of the cited references, whether considered individually or in combination, teach or suggest a method for assaying the angiogenic potential of a particular tumor from a mammal. Rather, the cited references are concerned with general angiogenesis models, or with methods for identifying compositions that tend to enhance or suppress angiogenesis generally.

But nowhere do any of the cited references teach or suggest a method for assaying the angiogenic potential of a particular tumor. Knowledge of the angiogenic potential of a particular tumor can be extremely beneficial in designing a treatment for an individual patient. Different patients may react differently to the same drug. A given tumor may react differently to two different drugs with the same mechanism of action. Sometimes different tumors within a single patient may react differently to the same drug. The present invention provides, for the first time, a means for assaying the angiogenic potential of a particular tumor. One advantage of the invention is that it may be used to determine a functional angiogenic index (as opposed to a histological angiogenic index) for a particular tumor. Tumors with a poor prognosis may be identified by their high functional angiogenic index, even though they may have a low histological angiogenic index. A disparity between functional and histological angiogenic indices may occur if circulating anti-angiogenic

substances (such as angiostatin/endostatin) mask the angiogenic potential of a tumor. The invention may also be used to develop prognostic tests for a patient's resistance or susceptibility to the future development of malignancy or angiogenesis-related diseases. (See generally the present specification at page 21, lines 5-14.)

By contrast, both Brown and the '782 Patent describe general angiogenesis models based on culturing isolated blood vessel fragments. As was discussed during the recent Interview, the development of new vessels around the periphery of such a fragment is a very different process from the extension of existing vessels from within the interior of a tumor sample having a substantially intact three-dimensional architecture.

Lugassy described a "rebuilt" tumor model, in which cells from a lymphoma cell line were mixed with angioma fibroblasts. The mixed cells were suspended in a collagen gel, which then grew into a "rebuilt" tumor model. Such a "rebuilt" tumor model neither teaches nor suggests any method for assaying the angiogenic potential of a particular tumor in a mammal.

Not only did Montesano's system not measure the angiogenic potential of any particular tumor, it did not even use tumor tissue. Rather, it used muscular tissue from the diaphragm of newborn rats, muscular tissue from the abdominal wall of adult rats, or adipose tissue from the epididymal fat pad of adult rats. (p. 870, first paragraph under "Materials and Methods"). As discussed in Applicants' prior responses, Montesano's samples were minced into small fragments. Applicants have previously argued why one could infer that these fragments were too small to preserve a substantially intact three-dimensional architecture, as required by Claim 1. The Office's previous replies have

expressed doubt over whether such an inference is justified. Even if this inference were mistaken -- even if Montesano's fragments were indeed large enough to preserve the three-dimensional architecture -- it would still be the case that nothing in Montesano teaches or suggests any method for assaying the angiogenic potential of a particular tumor. Rather, the purpose of Montesano's system was to provide a general model for the study of angiogenesis. As described in the words of Montesano *et al.*, the purpose was to provide "a simple in vitro model for the study of angiogenesis," (Abstract, p. 869; see also p. 872, third paragraph) or a model "to study the effect of factors which induce or inhibit angiogenesis or modulate endothelial cell behavior, as well as the role of proteolytic enzymes in the invasion of the extracellular matrix." (p. 874, citations omitted).

It is respectfully submitted that all prior art rejections should be withdrawn.

Supplement to Examiner Interview Summary under M.P.E.P. § 713.04

In accordance with M.P.E.P. § 713.04, the following remarks are presented to supplement the October 7, 2003 Examiner Interview Summary. Except as noted, Applicants concur in the Examiner Interview Summary.

The photographs shown by inventor Dr. Eugene Woltering included photomicrographs both of embodiments of the present invention, and of angiogenesis from a cultured blood vessel fragment.

The Examiner was given a copy of a paper published after the filing date of the present application, a paper that demonstrates the utility of certain aspects of the present invention: E. Woltering *et al.*, "Development of a novel in vitro human tissue-based

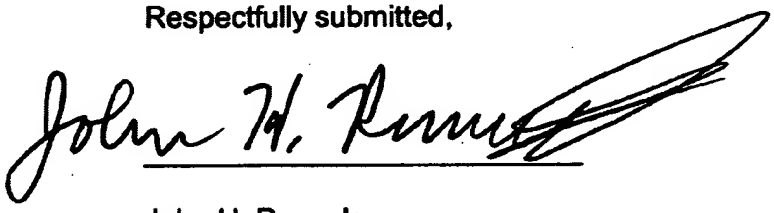
angiogenesis assay to evaluate the effect of antiangiogenic drugs," *Ann. Surg.*, vol. 237, pp. 790-800 (2003). The Examiner was also given an excerpt from a new manuscript that, among other things, discusses the differing effects of epothiolone-B and taxol on angiogenesis in samples from various tumors in accordance with the present invention.

The arguments presented and amendments discussed during the Interview were generally similar to those given in the present amendment.

Conclusion

It is respectfully submitted that all pending Claims are in condition for allowance. If the Office disagrees with any of these amendments or remarks, or if other issues arise that may present an obstacle to allowance, the undersigned would welcome a telephone call to discuss such matters before further action is taken. Otherwise, allowance of Claims 1-10, 13, 38, and 39 at an early date is respectfully requested.

Respectfully submitted,



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